A Pathophysiological Perspective on COVID-19's Lethal Complication: From Viremia to Hypersensitivity Pneumonitis-like Immune Dysregulation

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A Pathophysiological Perspective on COVID-19's Lethal Complication: From Viremia to Hypersensitivity Pneumonitis-like Immune Dysregulation

Marcos A. Sanchez-Gonzalez,[1] Dave Moskowitz,[2] Priya D. Issuree,[3,4] George Yatzkan,[5] Syed A. A. Rizvi,[1] and Kenneth Day[6]

[1]Division of Clinical & Translational Research, Larkin Health System, South Miami, Florida, USA.

[2]GenoMed, Leesburg, Florida, USA.

[3]Inflammation Program, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA.

[4]Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA.

[5]Intensive & Critical Care Unit, Larkin Health System, South Miami, FL, USA.

[6]Zymo Research Corporation, Irvine, California, USA.

Corresponding Author: Marcos A. Sanchez-Gonzalez, MD, PhD. VP for Research & Academic Affairs, Division of Clinical & Translational Research, 7000 SW 62nd Ave, Suite 601, South Miami, FL 33143, USA. Tel: +305-284-7608, Fax: +305-284-7545,

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus responsible for our recent coronavirus disease 2019 pandemic, is driving a lung immunopathology that strongly resembles a severe form of hypersensitivity pneumonitis (HP). A review of recent Severe acute respiratory syndrome-related coronavirus (SARS-CoV) and SARS-CoV-2 medical reports, as well as described characteristics of HP, lead us to postulate a theory for SARS-CoV-2 severe disease. We propose that the novel SARS-CoV-2 can act as a trigger and substrate of an HP-like severe immune reaction especially in genetically vulnerable individuals in addition to those with immune senescence and dysregulation. Accordingly, the purpose of our letter is to shift the emphasis of concern surrounding immune activity from viral infection to an HP-like severe immune reaction. We review similarities in disease presentation between infection and allergy, relevant immunopathology, and outline phases of SARS-CoV-2 disease with perspectives on therapy and critical care. Altogether, the favored course is to begin treatments that address the disease at the earliest phase before immune dysregulation leading to uncontrolled pulmonary inflammation.

Keywords:

Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Hypersensitivity pneumonitis; Genetic Susceptibility; Immune Dysregulation

A recent opinion report from Seoul, Korea suggested that the main lethal complication of the severe acute respiratory syndrome that results from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection, also known as coronavirus Disease 2019 (COVID-19), is manifesting as a form of hypersensitivity pneumonitis (HP) [1]. Severe SARS-CoV-2 begins much like mild or moderate cases with symptoms such dyspnea and cough, but may progress into a pneumonia-like disease with progression toward respiratory failure and pulmonary thrombosis [2]. These characteristics also resemble progression of HP with continued chronic exposure to antigen. Many of the common characteristics of COVID-19 such as chest tightness, cough, and dyspnea strongly overlap with features of HP [3]. A “two-hit” hypothesis has been suggested to promote HP, wherein preexisting genetic susceptibility or environmental factors (*i.e.*, the first hit) increases the risk for the development of HP after antigen exposure (the second hit). Over 300 substances (as the second hit) are known to act as triggers of HP such as avian-related antigens, birch wood with Gram-negative bacteria, molds, cheese, fungus, hay, and chemicals [4, 5, 6, 7]. Viral antigens can induce HP as influenza virus and coronavirus antigens are often found in bronchoalveolar lavage (BAL) cells and lung tissue of patients with HP that indicate a critical role of viruses as a trigger driving manifestation of the diesease [8, 9, 10]. We propose a theory that the novel COVID-19 can act as a trigger and substrate of an HP-like severe immune reaction especially in genetically vulnerable individuals and those with immune senescence and dysregulation. Chronic HP is typically managed by isolating the antigen that incites disease, and shortened survival was associated with inability to identify antigen [11]. If SARS-CoV-2 infection is viewed from the perspective that it is increased exposure to inciting antigen as an HP-like response leading to a severe immune reaction, this also changes perspectives on treatments.

HP is subdivided into acute, subacute, and chronic forms based on pathophysiology [12]. Acute HP is characterized by cough, chest tightness, dyspnea with neutrophilic infiltration, pulmonary fibrin formation, and thoracic computed tomography (CT) scan ground glass opacity (GGO) with reticulonodular pattern [13]. Acute HP symptoms such as fever and cough often resemble influenza, and continued exposure to an allergen can drive progression toward chronic disease [14]. Subacute HP displays similar symptoms as acute forms, except that the lung pathology escalates toward intersitial infiltrates with bronchiolitis and GGO exhibiting centriobular nodules [13, 15]. Chronic HP shows escalated symptoms with increased lymphocyte, mast cell, and eosinophil infiltration into the lungs with neutrophil activity. CT features in severe SARS-CoV-2 cases were described to have GGO associated with non-infectious lung conditions described as subpleural air-space disease with GGO features being detected even in the earliest mild asymptomatic patients [16]. However, while GGO and symptoms presentated together show similarity between severe SARS-CoV-2 and HP-like illness, these features alone cannot conclusively determine that they are the same disease as very often GGO cannot distinguish between infectious and non-infectious disease conditions [17]. In fact, chronic HP exhibit GGO that overlap with interstitial pneumonia, and therefore is commonly misdiagnosed as such [13, 18].

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Immunopathology

HP is a combination of type III and IV hypersensitivity directed toward allergen that drives the development of immune complexes with T cell activity that shifts toward a Th2 response [12]. With an increased presence of immune complexes, complement cascade activity is well established as a characteristic of HP [19, 20]. Interestingly, these features resemble the progress of severe SARS-CoV-2 disease [21]. Both chronic HP and SARS-CoV-2 can progress toward hyperinflammation in the lungs that may promote coagulation and thrombosis [2]. As a component of a Th2 response, eosinophil activity may be a “double-edged sword” also as a shared feature between respiratory virus infection and allergy. Eosinophils destroy ssRNA genomes of respiratory tract viruses through their ribonucleases via the TLR7 receptor [22]. TLR4 and TLR7 receptors balance Th1 and Th2 immunity [23]. SARS-CoV (SARS-CoV fullname) ssRNA signaling through TLR7 stimulated IL-6 and TNF expression almost 2-fold greater than other viruses [24]. IL-6 strongly predicts severe SARS-CoV-2 cases and is a major target for blocking downstream macrophage activation syndrome [25]. IL-4 and IL-13 signaling among mast cell activity recruits eosinophils from the bone marrow into the lung through IL-5, a cytokine required for clearance of virus and detected in severe SARS-CoV-2 patients [26, 27, 28]. Mast cells were 1000-fold higher in BAL of HP patients, and analysis of excessive amounts of histamine in the fluid suggested that the lavage procedure may promote mast cell degranulation [29]. In this vein, eosinopenia in severe SARS-CoV-2 cases and may suggest migration to the lungs [30]. Autopsy has confirmed eosinophils in the lung, and restoration of eosinophil counts in the blood are predictive of SARS-CoV-2 resolution by also testing negative via reverse transcription polymerase chain reaction (RT-PCR) signifying viral clearance [31, 32]. Blood eosinophil levels with increased neutrophil to lymphocyte ratio were linked to severe patients that remained in the intensive care unit (ICU) while remaining RT-PCR positive [33, 34]). Elevated NK and NKT cells were positively correlated with eosinophils among interstitial lung diseases that include HP [35].

Besides HP, shared immune activity between infection and other allergic airway inflammation is well established. Asthma induction in children is strongly linked to hypersensitivity response to Respiratory Syncytial Virus (RSV), while in older individuals, asthma may be connected to rhinovirus [36, 37]. Virulent pneumonia virus of mice (PVM) is not well cleared by eosinophils and may actually better represent acute respiratory distress syndrome (ARDS) caused by RSV infection in humans [38]. PVM-infected mice show rapid replication with eosinophilic response, granulocyte recruitment, edema,

inflammation, respiratory failure, and death [39]. *TMPRSS2* and *ACE2* are the two main host genes required for SARS-CoV-2 entry into cells, and ACE2 is the receptor for the SARS-CoV-2 spike protein (PMID: 32142651). Recent work among 695 asthmatic and healthy child cases showed that *TMPRSS2* expression was upregulated by the Th2 response, while *ACE2* was downregulated, and suggested that low-level airway inflammation may be protective against SARS-CoV-2 infection [40]. Asthma comorbitity is far less frequent among other comorbidities in SARS-CoV-2 severe cases [41]. It is possible that asthmatics may self-treat with inhaled prescription corticosteroids upon symptoms accompanying SARS-CoV-2 infection. Altogether, poor outcomes during hypersensitivity reactions leading to ARDS may coalesce with mechanisms to clear viral infection.

Poor eosinophilic anti-viral activity among more virulent respiratory infections may be a part of disease initiation [42]. For instance, Vaccination alone of many respiratory viruses induced pulmonary eosinophilia and enhanced lung disease with hypersensitivity upon challenge of infection [43]. Macaques vaccinated with human metapneumovirus and challenged also developed eosinophilic pathology and hypersensitivity [44]. As expected, candidate SARS-CoV vaccines tested in animals also exhibited the same Th2 lung immunopathology [45]. Similar immunopathology in mice was replicated, and also showed that the nucleocapsid alone could trigger the hypersensitivity response with very poor outcomes for aged mice [46]. Collectively, this raised safety concerns for the double inactivated SARS-CoV vaccine in the elderly [46], and also suggested that eosinophils may contribute to early immune dysregulation independent of their anti-viral activity.

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Poor outcomes and genetic susceptibility

Similar to chronic disease manifestations in HP, poor outcomes of SARS-CoV-2 severity include fibrosis and lung injury [47]. Expression of *TMPRSS2* was also associated with other gene expression enriched in mucus goblet cell markers within the lung and eosinophil levels were suggested as a proxy measurement for Th2 airway inflammation and severity of outcomes [40]. While the environmental triggers associated with HP have been extensively studied, the contribution of genetics in disease progression is still not well understood. A variant rs35705950 located near MUC5B could contribute to risk for severe and moderate chronic HP using metrics of fibrosis measured by CT, and comparisons to healthy controls yielded odds ratios of 2.27 to 3 [48, 49]. Poor outcomes in chronic HP were more strongly associated with telomeropathy. Variants in telomere-related genes were associated with shorter peripheral blood telomere lengths in a discovery and replication cohort with age, sex and ancestry adjustment containing a hazard ratio of 3.73, and there were significant differences in survivorship according to telomere lengths stratified by the 10th percentile for age [50, 51]. Telomere length is also associated with other interstitial lung diseases with pulmonary fibrosis in peripheral blood, but not within lung tissue [52]. Since telomeres typically shorten with age, but different rates of shortening may allow for measuring chronological versus biological aging and SARS-CoV-2 severe cases have a strong connection to aging, it would be interesting to measure association with telomere length, especially in younger patients with severe disease.

Mouse models of HP recently identified a QTL on chromosome 18 implicating the candidate gene *Cdh2* with corroborating evidence of cadherin 2 upregulation in the lungs of chronic HP-induced mice that may be indicative of epithelial to mesenchymal transition responsible for progression toward fibrosis [53]. fibrotic disease is also typically associated with progression toward hypercoagulation [54], and this is a feature of SARS-CoV and SARS-CoV-2 severe disease as well. Memory Th2 cells may promote airway inflammation and fibrosis through the reprogramming of eosinophils to upregulate the production of osteopontin, or SPP1 [55]. A recent single-cell RNA-seq study of mild and severe SARS-CoV-2 BAL

samples showed SPP1 was elevated as distinguishing gene expression marker in severe versus mild disease [56]. Currently, there are no genome-wide studies available for host genotype on the severity of SARS-CoV-2, but analysis of these discussed loci in the context of severe HP may be a starting point. However, the allele rs12252 located near the IFITM3 gene was associated with severe versus mild SARS-CoV-2 cases of Asian ancestry with odds ratio of 11.67 and 6.37 with adjustment for age [57]. IFITM3, which is expressed in $CD4^+$ T cells, and was downregulated during activation confers protection against a variety of viruses that include RSV and SARS-CoV as an absence of these genes in mice reduced eosinophilia and was protective against allergy and asthma [58, 59].

Based on the overlap in cell and molecular immunopathology, it seems reasonable to suggest that the disease manifesting itself as COVID-19 may immune dysregulation driven by an HP-like severe immune response triggered by the excessive viral load as secondary to the infection [1]. Understanding the role of eosinophils could be the key to understanding the disease as a hypersensitivity-like response [60]. More studies require autopsy reports, collections of BAL, and animal models to better characterize the similarities between HP-like disease and SARS-CoV-2 severity. Our observations should be an important consideration for the development of vaccines for SARS-CoV-2 [61], and also provides an opportunity to treat patients early. For HP itself, often the inability to determine the offending antigen is strongly associated with poor survivorship [11]. With the perspective that SARS-CoV-2 virus may drive HP-like immune dysregulation, it might be possible to prevent systemic severe hyper-cytokinemic inflammatory state or cytokine storm that results in macrophage activation syndrome [62].

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Phases from viremia to hypersensitivity pneumonitis-like severe immune response

1. Phase I

Based on the clinical features, vaccine studies of SARS-CoV, and similarities to HP, an aggressive blockage of allergic and hypersensitivity responses could be of clinical relevance in the treatment of COVID-19. One potential therapeutic approach could be to block Mast cell and EOS responses early in the course of the COVID-19 infection (days 2 - 5) defined here as *Phase I* **(**EOS and NEU/LYM baseline). As the viral load increases so do the allergen/antigens creating a similar environment to the pathophysiology of HP. Interestingly, chest X-ray findings in COVID-19 patients are consistent with those of HP including the most important complication, lung fibrosis [63, 64]. Mast cell stabilizers (*i.e.* β2-adrenergic agonists, Cromoglicic acid, Ketotifen) and eosinophil blocking agents (*i.e.* Omalizumab, Mepolizumab) could key players in delaying or preventing the lethality of the SARS-CoV-2-induced hypersensitivity-like response.

2. Phase II

As COVID-19 progresses, 5 - 9 days into disease, EOS "migrate to the lungs" and hence the marked decrease in the blood *Phase II* **(**Blood Count Finding; ↓EOS and ↑NEU/LYM). The Phase II response is consistent with histopathology seen in animals given the SARS-CoV vaccines displaying Th2-type immunopathology with prominent EOS infiltration [45]. Interestingly, allergic patients and asthmatics typically use medications that control these adverse responses in the first place which may lead to no severe co-morbidity cases of asthma patients as suggested by current reports [41, 63].

3. Phase III

Once the SARS-CoV-2-induced HP-like severe immune response is fully active, respiratory distress syndrome, the lungs get affected by uncontrolled inflammation, fluid accumulation, lymphocyte-dominant interstitial inflammatory cell infiltration, progressive fibrosis will begin to severely compromise the gas exchange, acute *Phase III* (↓LYM) [65]. As pneumocyte dysfunction installs, owing to both viral infectivity and increased immune hypersensitive response, there is a decrease in the production of surfactant inducing impaired gas exchange [66]. These findings are consistent with reports describing CT impressions and pulmonary fibrosis in COVID-19 survivors and [67, 68]. Increased fluid in the lungs and less oxygen in the circulation leads to increased myocardial right ventricular work and oxygen consumption that become an advanced critical complication for those with cardiac conditions. It is plausible that the use of anticoagulant administration in Phase III may ameliorate the diffusion problem and improve oxygen saturation as a severe complication is the development of pulmonary thromboembolism that have been reported in HP [69]. Noteworthy, many of the aforementioned findings are consistent with those of severe interstitial pulmonary disease or late chronic HP in which neither non-invasive ventilation nor invasive mechanical ventilation seems to change the poor outcomes associated with advanced stages [70]. Patients diagnoses with COVID-19 that are under ventilatory support have been reported to have the highest mortality.

In summary, COVID-19 complication and progression may take three phases that mimic HP as the virus is simultaneously the substrate and trigger of the altered immune response and ARDS. Prospective therapeutic strategies aimed at identifying those individuals that are genetically susceptible as well as hypersensitive individuals might decrease the main complications of the disease. Furthermore, the earlier the disease is recognized as a hypersensitive-like response, the quicker it can be treated at earlier phases to prevent progression into severe disease (Table 1). Research studies designed to understand the underlying mechanisms accountable for the HP-like severe immune response in severely ill COVID-19 patients are warranted.

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Author Contributions:

- **Conceptualization:** MASG, KD.
- **Writing - original draft:** MASG, DM, PDI, GY, SAAR, KD.
- **Writing - review & editing:** MASG, DM, PDI, GY, SAAR, KD.

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